Supplementary Data

Predicting cardiac electrical response to sodium channel blockade and Brugada syndrome using polygenic risk scores

Short title: Genetic prediction of cardiac sodium-channel blockade

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Single SNP association analysis

Methods

For PR and QRS slopes and BrS ECG, single SNP genome-wide association analysis was performed using a linear mixed model accounting for relatedness estimated with a genetic relatedness matrix for each chromosome, leaving one chromosome out, as implemented in GCTA.[23]

Results

No associations were uncovered for PR or QRS slopes at genome-wide statistical significance (i.e. $P<5x10^{-8}$) (**Supplementary Figure 5**, **A** and **B**). The result of the case-control genome-wide association analysis of the drug-induced type I BrS ECG including 431 ajmaline-positive cases and 922 ajmaline-negative controls is presented as a Manhattan plot in **Supplementary Figure 5C** and quantile-quantile plot in **Supplementary Figure 6**. The *SCN5A-SCN10A* locus previously associated with BrS itself[13] was also strongly associated with the development of ajmaline-induced type I BrS ECG ($P=8.6x10^{-19}$). The lead SNP rs10428132 shows a higher frequency of the BrS risk allele [T] in cases with an ajmaline-induced type I ECG (0.60) vs. controls without an induced type I ECG (0.41), associated with an odds ratio of 2.1 per risk allele. The P-values of single SNP associations of previously published SNPs in PR, QRS and BrS with PR slope, QRS slope and ajmaline-induced type I ECG, respectively, are listed in **Supplementary Table 3**. The combination of these multiple SNPs with small effect sizes is the foundation underlying the use of PRS to predict the response to ajmaline, described in the main manuscript.

Supplementary Table 1: SNPs and effect sizes used to calculate PRS_{BrS}, PRS_{PR} and PRS_{QRS}

dbSNP ID	Cytoband	Chromosome	Genomic position (GRCh37)	Reference allele	Alternate allele	Beta (alternate allele)	P-value in prior GWAS	Reported genes
PR interval GWAS (van Setten et al[19]) for PRS_{PR}								
rs4648819	1p36.33	1	2204790	G	A	1.7	4.68E-10	*SKI*
rs7538988	1p32.3	1	51817541	T	C	-2.1	1.14E-08	*EPS15*
rs12127701	1p13.3	1	109838264	A	G	1.7	1.54E-09	*MYBPHL, SYPL2*
rs11264339	1q22	1	155140648	C	T	-0.7	5.94E-10	*ADAM15*
rs397637	1q42.13	1	228453328	G	T	0.8	7.11E-10	*OBSCN*
rs3856447	2p25.1	2	8750266	A	G	-1.2	1.20E-26	*ID2*
rs4430933	2p14	2	66749610	A	G	-1.3	5.06E-30	*MEIS1*
rs2732860	2q12.1	2	103398334	G	A	0.9	3.03E-15	*TMEM182*
rs13018106	2q24.3	2	164375202	G	C	-0.8	1.53E-11	*FIGN*
rs922984	2q31.2	2	179615887	T	C	-1.5	1.79E-11	*TTN*
rs9826413	3p24.1	3	27834747	A	T	2	1.69E-08	*EOMES*
rs11708996	3p22.2	3	38633923	G	C	3.1	1.06E-68	*SCN5A*
rs6599250	3p22.2	3	38784029	T	C	-3.8	4.42E-242	*SCN10A*
rs900669	3p14.1	3	69406802	T	A	0.8	5.71E-09	*FRMD4B*
rs13087058	3p13	3	73551228	T	C	-1	5.82E-17	*PDZRN3*
rs16858828	3q13.2	3	111630787	A	C	0.9	2.41E-08	*PHLDB2*
rs6441111	3q25.31	3	156821808	C	T	-0.8	6.96E-11	*CCNL1*
rs7638853	3q27.2	3	185350706	G	A	-0.7	2.44E-08	*SENP2*
rs343849	4q21.23	4	86663055	A	T	2.1	3.12E-61	*ARHGAP24*
rs17446418	4q26	4	114418006	T	G	0.8	3.41E-09	*CAMK2D*
rs3733409	4q35.2	4	187627593	C	T	0.9	2.67E-08	*FAT1*
rs7729395	5q21.1	5	102100576	C	T	2.4	1.00E-10	*PAM*
rs255292	5q35.1	5	172580866	C	A	1.1	5.99E-21	*BNIP1, NKX2-5, CREBRF*
rs11763856	7p14.2	7	35545787	C	T	3.1	4.47E-10	*TBX20, HERPUD2*
rs3807989	7q31.2	7	116186241	A	G	-2	8.65E-69	*CAV1, CAV2*
rs2129561	7q32.3	7	130963771	A	G	1	3.39E-15	*MKLN1*
rs881301	8p11.22	8	38332318	T	C	0.8	5.04E-10	*FGFR1*
rs12678719	8q23.1	8	106516054	C	G	0.8	3.77E-10	*ZFPM2*
rs12359272	10q24.1	10	97365163	G	A	1	3.68E-16	*ALDH18A1, SORBS1*
rs12257568	10q24.33	10	105522875	C	T	1	5.83E-18	*SH3PXD2A, OBFC1*
rs1372797	11p15.1	11	20015276	G	T	-1.1	2.36E-09	*NAV2*
rs652673	11q13.5	11	75931291	C	T	0.8	4.41E-08	*WNT11*
rs17287293	12p12.1	12	24770878	A	G	-2.2	2.33E-41	*C12orf67, SOX5*
rs6489953	12q24.21	12	114764762	C	T	-1.2	1.94E-16	*TBX5*
rs1896312	12q24.21	12	115346424	C	T	-1.6	1.16E-34	*TBX3*

rs11067773	12q24.21	12	116228495	T	C	-1.3	1.02E-08	*MED13L*
rs2585897	13q12.11	13	21398979	G	A	1.2	9.28E-16	*XPO4*
rs718426	13q12.11	13	22085659	A	G	-1.2	3.25E-24	*EFHA1*
rs9590974	13q14.13	13	47238717	C	A	-1.1	1.02E-19	*LRCH1*
rs11465506	14q11.2	14	23842661	G	A	-6.4	7.06E-10	*IL25,MYH6*
rs4901308	14q22.1	14	53379925	T	C	0.8	2.04E-08	*FERMT2*
rs17767398	14q24.2	14	71770485	C	G	1	6.44E-13	*SNORD56B, SIPA1L1*
rs904974	15q23	15	70447582	T	C	-1.1	4.53E-08	*TLE3*
rs1984481	17p12	17	12637742	G	C	-0.8	1.37E-11	*MYOCD*
QRS duration (van der Harst et al[20]) for PRS_{QRS}								
rs17391905	1p32.3	1	51546140	T	G	-1.27	1.07E-11	*CDKN2C*
rs2207790	1p31.3	1	61897967	G	A	-0.55	6.71E-19	*NFIA*
rs12039739	1p13.1	1	116333111	C	T	-0.41	6.22E-10	*CASQ2*
rs3770770	2p22.2	2	37192866	C	T	0.49	4.95E-11	*STRN*
rs6801957	3p22.2	3	38767315	T	C	-0.77	6.90E-40	*SCN10A, SCN5A*
rs4687718	3p21.1	3	53282303	A	G	0.57	6.70E-10	*TKT*
rs2242285	3p14.1	3	66431602	A	G	-0.34	5.65E-09	*LRIG1, SLC25A26*
rs1344852	4p15.31	4	20183937	G	C	0.46	1.45E-09	*SLIT2*
rs13165478	5q33.2	5	153869040	G	A	-0.59	8.06E-19	*HAND1*
rs1321311	6p21.31	6	36622900	C	A	0.84	1.03E-37	*CDKN1A*
rs11153730	6q22.31	6	118667522	T	C	0.63	7.44E-29	*SLC35F1, PLN, CEP85L*
rs1419856	7p14.3	7	35306983	A	G	0.67	6.67E-18	*TBX20*
rs6968945	7p12.3	7	46640900	C	T	-0.34	5.14E-09	*TNS3*
rs11773845	7q31.2	7	116191301	C	A	-0.36	7.50E-10	*CAV1, CAV2*
rs1194743	10q21.1	10	54212597	T	C	-0.44	5.87E-09	*DKK1*
rs7918405	10q25.2	10	114505465	G	A	0.5	1.05E-14	*VTI1A*
rs174577	11q12.2	11	61604814	C	A	-0.38	4.79E-12	*FADS2, TMEM258*
rs883079	12q24.21	12	114793240	C	T	-0.52	4.58E-16	*TBX3*
rs728926	13q22.1	13	74513122	C	T	-0.4	5.60E-11	*KLF12*
rs12880291	14q24.2	14	71884567	G	T	-0.49	4.41E-14	*SIPA1L1*
rs17608766	17q21.32	17	45013271	T	C	0.52	8.98E-09	*MAPT, KANSL1*
rs9910355	17q24.2	17	64315205	A	C	-0.41	1.14E-11	*PRKCA*
rs879568	18q12.2	18	34311659	G	C	-0.34	1.88E-09	*FHOD3*
rs10853525	18q12.3	18	42436652	C	T	0.46	1.41E-14	*SETBP1*
rs2025096	20q11.22	20	33540000	G	A	-0.37	4.08E-09	*GSS, EDEM2, MYH7B*
rs13047360	21q21.3	21	28851580	A	G	0.47	4.02E-10	*ADAMTS5*
BrS GWAS (Bezzina et al[13]) for PRS_{BrS}								
rs11708996	3p22.2	3	38633923	G	C	0.55	1.02E-14	*SCN5A*
rs10428132	3p22.2	3	38777554	T	G	-0.94	1.01E-68	*SCN10A*
rs9388451	6q22.31	6	126090377	T	C	0.46	5.14E-17	*NCOA7, HEY2*

Supplementary Table 2: Basic characteristics of included patients

	Total cohort (N=1368)*	Ajmaline test positive for a type I BrS ECG (N=431)	Ajmaline test negative for a type I BrS ECG (N=922)	P-value (positive vs. negative)
Male sex	691 (50.5%)	216 (50.1%)	475 (51.5%)	0.64
Age at ajmaline infusion	43.2±14.6	44.5±13.6	42.5±14.9	0.017
Pathogenic or likely pathogenic *SCN5A* variant/*SCN5A* tested	64/415 (15%)	48/245 (19.6%)	16/170 (9.4%)	0.00096
Infused dose (mg)	77.3±19.2	71.1±23.3	80.4±16.0	<0.0001
Infused dose (mg/kg)	1.0[1.0-1.1]	1.0[0.8-1.1]	1.0[1.0-1.1]	<0.0001
Test indication				<0.0001
Unexplained VF	40 (2.9%)	10 (2.3%)	29 (3.1%)	
FHx BrS	601 (44%)	215 (50%)	377 (41%)	
FHx SCD	491 (36%)	78 (18%)	411 (45%)	
Suspicious ECG	149 (11%)	105 (24%)	41 (4.4%)	
Syncope	32 (2.3%)	15 (3.5%)	17 (1.8%)	
Other	55 (4.0%)	8 (1.9%)	47 (5.1%)	

*Of the 1368 ajmaline infusion tests performed, 15 had an inconclusive BrS result. BrS, Brugada syndrome; FHx, family history of; SCD, sudden cardiac death; VF, ventricular fibrillation

Supplementary Table 3: Association of PRS SNPs with PR or QRS slopes and type I BrS ECG

dbSNP ID	Chromosome	Genomic position (GRCh37)	Reported gene	P-value
PR SNPs[19]				**PR slope**
rs4648819	1	2204790	*SKI*	NA
rs7538988	1	51817541	*EPS15*	0.705
rs12127701	1	109838264	*MYBPHL, SYPL2*	0.689
rs11264339	1	155140648	*ADAM15*	0.992
rs397637	1	228453328	*OBSCN*	0.544
rs3856447	2	8750266	*ID2*	NA
rs4430933	2	66749610	*MEIS1*	0.817
rs2732860	2	103398334	*TMEM182*	**0.029**
rs13018106	2	164375202	*FIGN*	0.550
rs922984	2	179615887	*TTN*	0.771
rs9826413	3	27834747	*EOMES*	0.414
rs11708996	3	38633923	*SCN5A*	0.273
rs6599250	3	38784029	*SCN10A*	**0.021**
rs900669	3	69406802	*FRMD4B*	0.065
rs13087058	3	73551228	*PDZRN3*	NA
rs16858828	3	111630787	*PHLDB2*	0.381
rs6441111	3	156821808	*CCNL1*	0.381
rs7638853	3	185350706	*SENP2*	0.428
rs343849	4	86663055	*ARHGAP24*	0.565
rs17446418	4	114418006	*CAMK2D*	0.825
rs3733409	4	187627593	*FAT1*	0.226
rs7729395	5	102100576	*PAM*	0.325
rs255292	5	172580866	*BNIP1, NKX2-5, CREBRF*	0.214
rs11763856	7	35545787	*TBX20, HERPUD2*	0.561
rs3807989	7	116186241	*CAV1, CAV2*	0.916
rs2129561	7	130963771	*MKLN1*	0.574
rs881301	8	38332318	*FGFR1*	0.875
rs12678719	8	106516054	*ZFPM2*	NA
rs12359272	10	97365163	*ALDH18A1, SORBS1*	0.399
rs12257568	10	105522875	*SH3PXD2A, OBFC1*	0.745
rs1372797	11	20015276	*NAV2*	0.895
rs652673	11	75931291	*WNT11*	0.752
rs17287293	12	24770878	*C12orf67, SOX5*	0.193
rs6489953	12	114764762	*TBX5*	0.913
rs1896312	12	115346424	*TBX3*	0.168

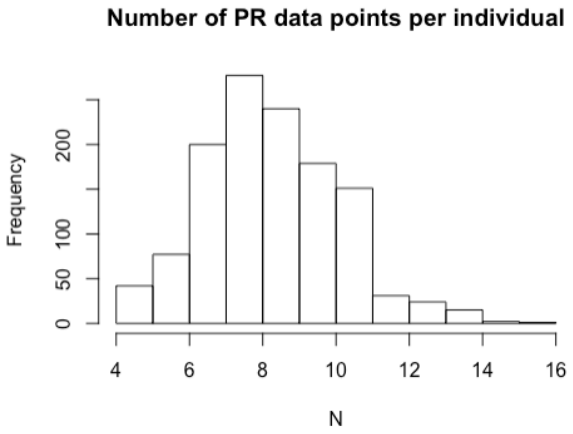
rs11067773	12	116228495	*MED13L*	0.325
rs2585897	13	21398979	*XPO4*	0.654
rs718426	13	22085659	*EFHA1*	0.729
rs9590974	13	47238717	*LRCH1*	0.579
rs11465506	14	23842661	*IL25, MYH6*	0.722
rs4901308	14	53379925	*FERMT2*	0.111
rs17767398	14	71770485	*SNORD56B, SIPA1L1*	NA
rs904974	15	70447582	*TLE3*	0.663
rs1984481	17	12637742	*MYOCD*	NA
QRS SNPs[20]				**QRS slope**
rs17391905	1	51546140	*CDKN2C*	**0.027**
rs2207790	1	61897967	*NFIA*	0.530
rs12039739	1	116333111	*CASQ2*	0.721
rs3770770	2	37192866	*STRN*	0.456
rs6801957	3	38767315	*SCN10A, SCN5A*	**0.043**
rs4687718	3	53282303	*TKT*	0.764
rs2242285	3	66431602	*LRIG1, SLC25A26*	0.148
rs1344852	4	20183937	*SLIT2*	0.879
rs13165478	5	153869040	*HAND1*	0.847
rs1321311	6	36622900	*CDKN1A*	**0.012**
rs11153730	6	118667522	*SLC35F1, PLN, CEP85L*	**0.014**
rs1419856	7	35306983	*TBX20*	0.949
rs6968945	7	46640900	*TNS3*	0.539
rs11773845	7	116191301	*CAV1, CAV2*	0.808
rs1194743	10	54212597	*DKK1*	0.297
rs7918405	10	114505465	*VTI1A*	0.395
rs174577	11	61604814	*FADS2, TMEM258*	0.152
rs883079	12	114793240	*TBX3*	0.449
rs728926	13	74513122	*KLF12*	0.976
rs12880291	14	71884567	*SIPA1L1*	0.088
rs17608766	17	45013271	*MAPT, KANSL1*	0.342
rs9910355	17	64315205	*PRKCA*	0.604
rs879568	18	34311659	*FHOD3*	0.838
rs10853525	18	42436652	*SETBP1*	0.513
rs2025096	20	33540000	*GSS, EDEM2, MYH7B*	0.121
rs13047360	21	28851580	*ADAMTS5*	0.388
BrS SNPs[13]				**Ajmaline-induced BrS ECG**
rs11708996	3	38633923	*SCN5A*	**1.06E-05**
rs10428132	3	38777554	*SCN10A*	**1.34E-18**
rs9388451	6	126090377	*NCOA7, HEY2*	**0.014**

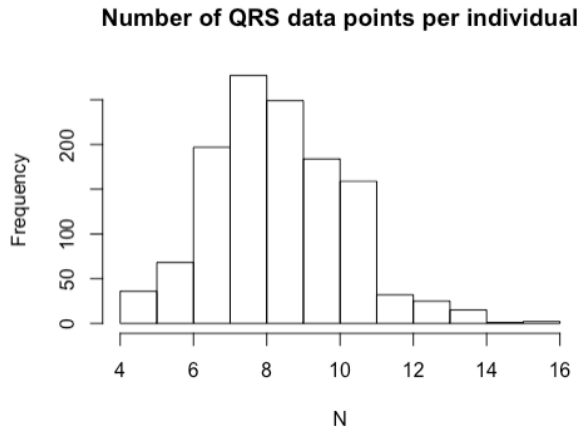
Supplementary Table 4: Multivariable analysis of PR slope, QRS slope and BrS type I ECG including *SCN5A* mutation status in the model

Predicted phenotype	Sample size	Predictors	Regression coefficient (standard error)	P-value
PR slope	291	Female sex	1.7 (1.7)	0.32
		PRS_{PR}	-0.20 (0.16)	0.21
		Baseline PR	0.08 (0.03)	0.006
		SCN5A mutation	6.0 (2.6)	0.02
QRS slope	295	Age (yr)	0.10 (0.06)	0.09
		PRS_{QRS}	0.39 (0.49)	0.43
		SCN5A mutation	21.0 (2.3)	<2E-16
BrS ECG	292	QRS	0.0018 (0.0028)	0.53
		PRS_{BrS}	0.17 (0.03)	0.000002
		FHx-BrS	-0.03 (0.07)	0.64
		Type II/III ECG	0.14 (0.07)	0.047
		SCN5A mutation	0.14 (0.09)	0.11

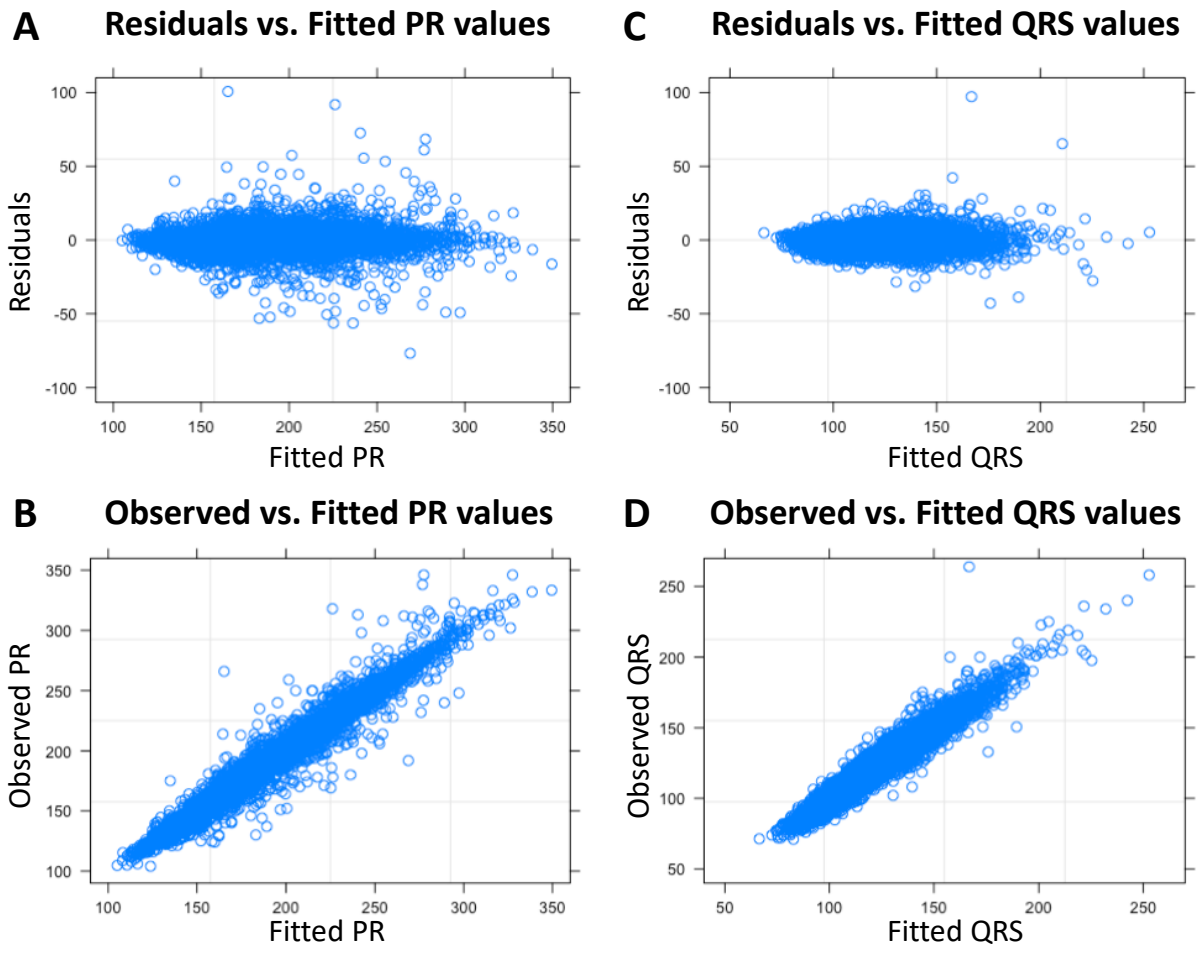
FHx-BrS, Family history of Brugada syndrome.

Supplementary Figure 1: Histograms of number of PR or QRS data points per sample

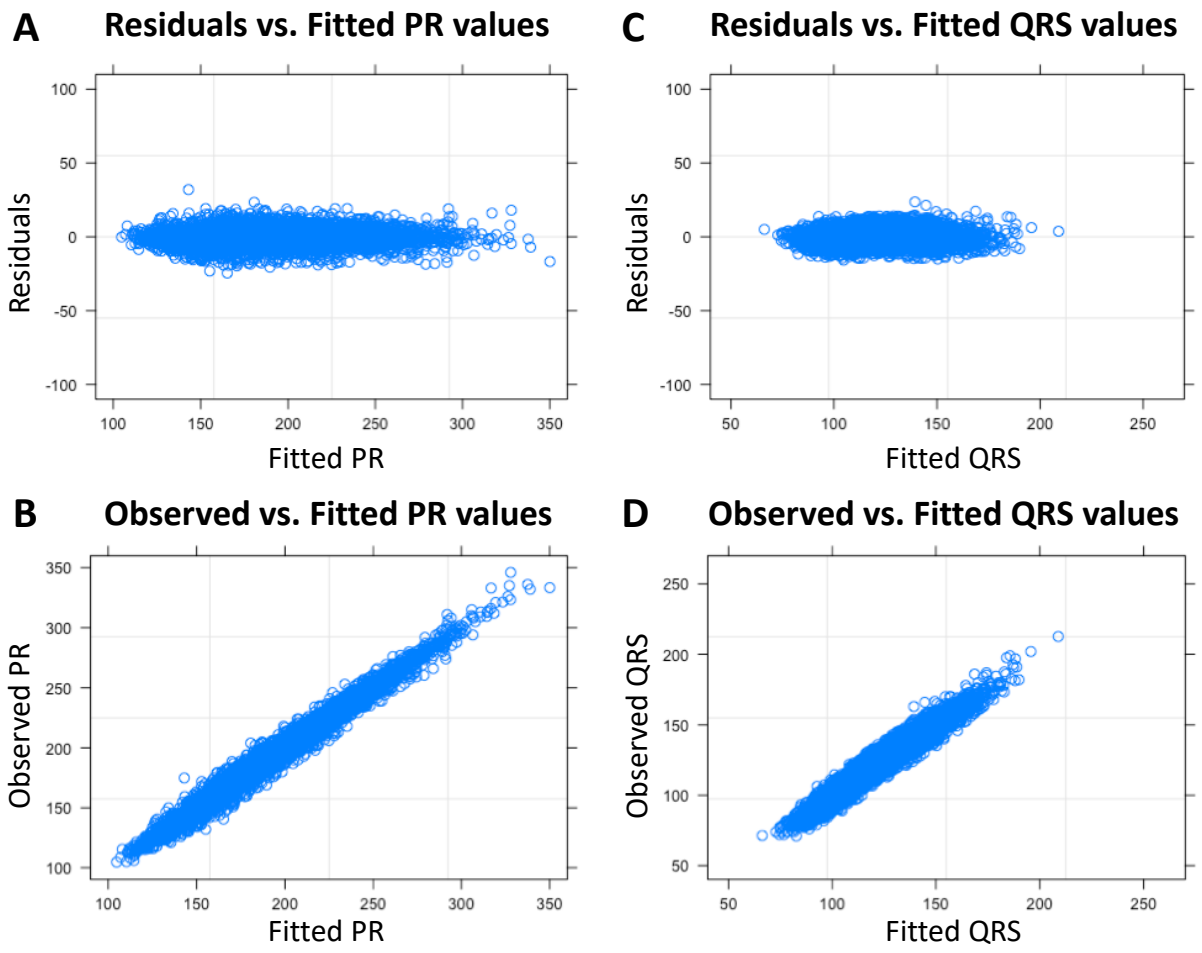




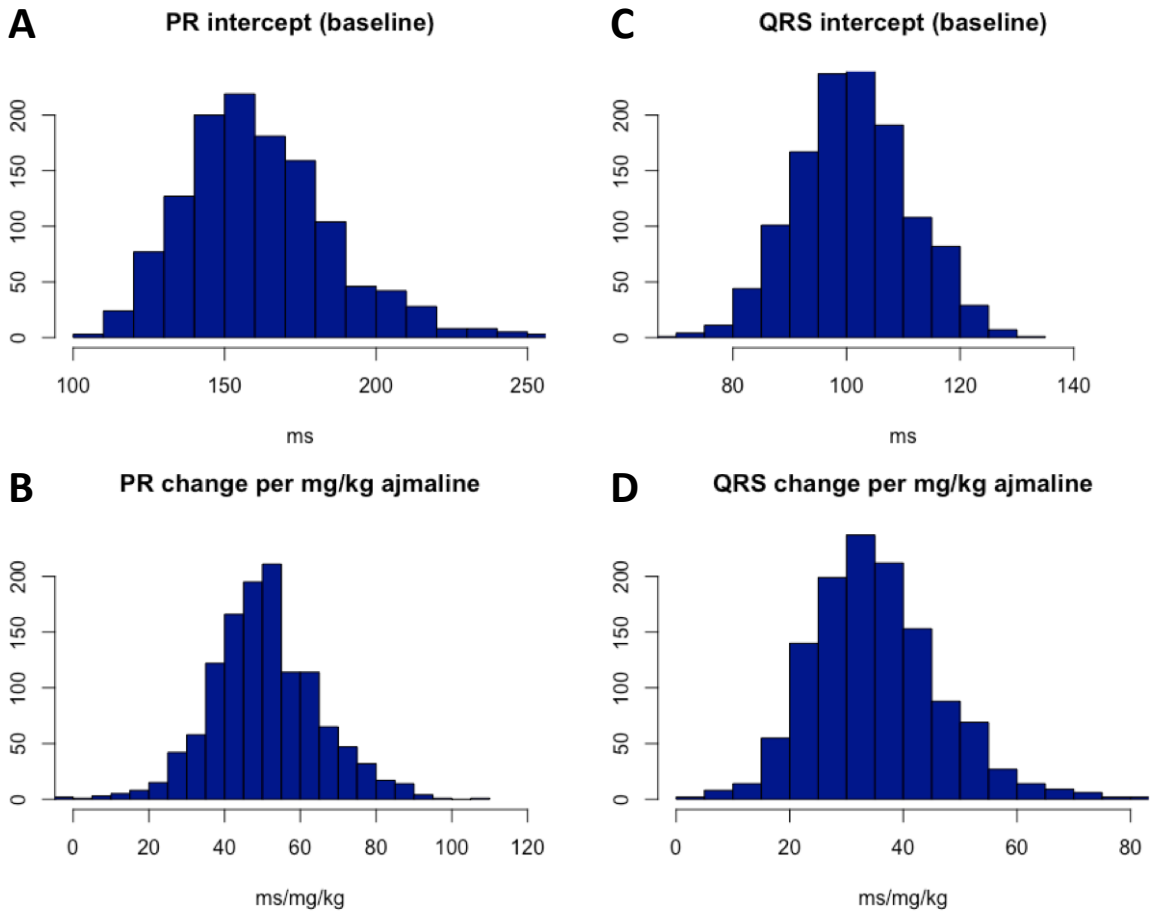
Supplementary Figure 2: Linear mixed modeling results of ajmaline dose-response on PR and QRS before marker correction. Panels **A** and **B** represent residuals vs. fitted values and observed vs. fitted values, respectively, for PR interval. Panels **C** and **D** show the same for QRS duration.



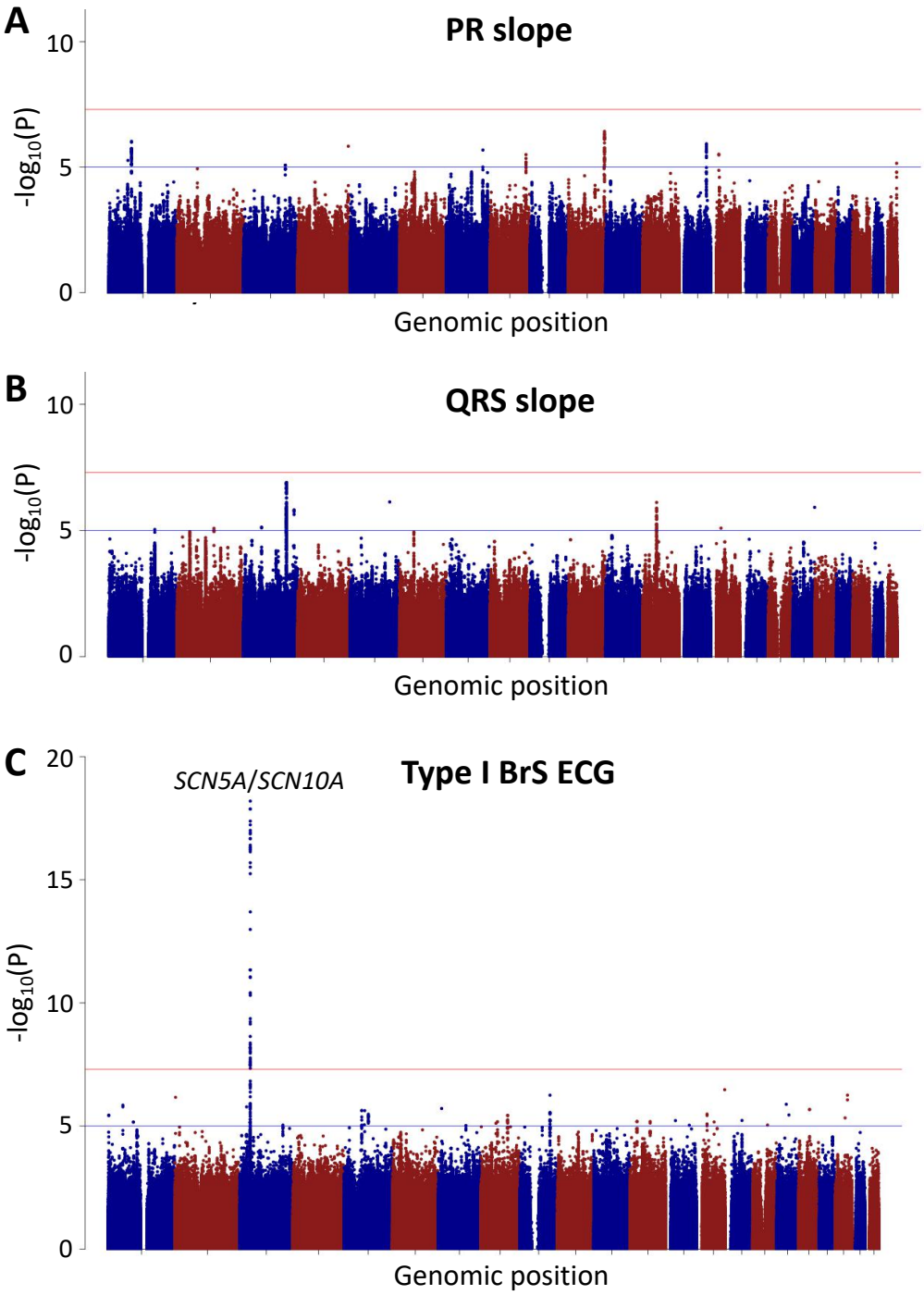
Supplementary Figure 3: Linear mixed modeling results of ajmaline dose-response on PR and QRS after marker correction. Panels **A** and **B** represent residuals vs. fitted values and observed vs. fitted values, respectively, for PR interval. Panels **C** and **D** show the same for QRS duration.



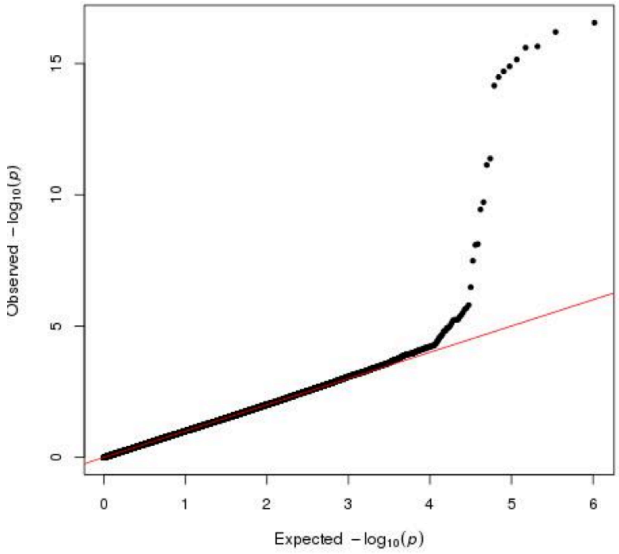
Supplementary Figure 4: Histograms of intercepts and slopes for PR (**A** and **B**, respectively) and QRS (**C** and **D**, respectively).



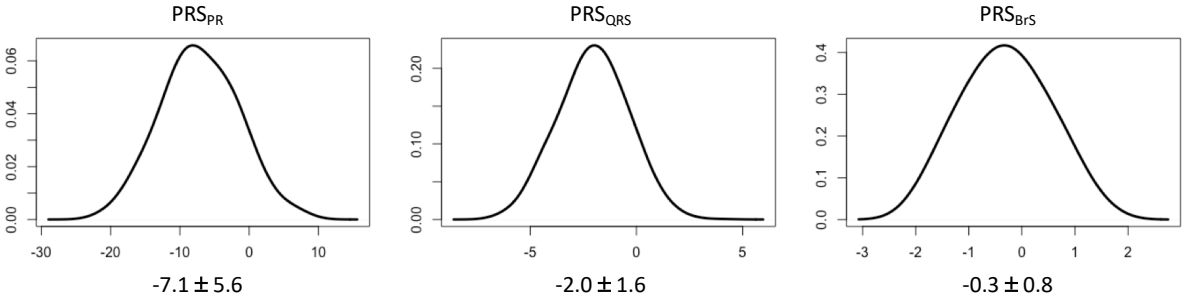
Supplementary Figure 5: Manhattan plots of linear mixed model association of PR slope (**A**), QRS slope (**B**) and ajmaline-induced type I ECG (**C**). Red and blue horizontal lines represent the genome-wide significance ($P<5\times10^{-8}$) and suggestive significance ($P<10^{-5}$), respectively



Supplementary Figure 6: Quantile-quantile (QQ) plot for single SNP association with ajmaline-induced type I BrS ECG using linear mixed modeling.



Supplementary Figure 7: Density plots of PRS_{PR}, PRS_{QRS} and PRS_{BrS}. Corresponding means ± standard deviations are shown at the bottom of each plot.



Supplementary Figure 8: Receiver operating classifier (ROC) curve for ajmaline-induced BrS based on PRS_{BrS} alone (**A**) and when combined with family history of BrS (FHx BrS), baseline QRS duration, and the presence of a baseline type II or III BrS ECG (**B**). C-statistic and its 95% confidence intervals (CI) are shown for each model.